REMARKS

After the above amendments, Claims 48-68 are pending.

A. Claim Of Priority

The Examiner states that this application fails to include the proper reference back to its priority applications. However, Applicants note that in the original transmittal papers, there is an express amendment to make appropriate reference in the specification to the priority applications. Nonetheless, Applicants have amended that Cross Reference to Related Application to explicitly state "PCT application PCT/US99/22746 claims priority from U.S. application Serial No. 09/165,961 and from U.S. provisional application Serial No. 60/102,962, also filed on October 2, 1998."

B. Election/Restrictions

The Examiner indicates that Claims 54-55, 59, 62 and 65 are withdrawn from further consideration as being drawn to a non-elected invention. However, those claims are within the elected group of Group I (Claims 48-68). Applicants request confirmation by the Examiner that Claims 54-55, 59, 62 and 65 are under consideration at this time.

C. Section 112 Rejection

Claim 48 has been rejected as being indefinite. Applicants traverse this rejection in part.

First, it is the Examiner's position that Claim 48 is indefinite because there is no antecedent basis for the use of "modified albumin" in line 8. It is submitted that the above amendment of Claim 48 overcomes this portion of the rejection.

It is also the Examiner's position that Claim 48 is indefinite for reciting an improper Markush group. However, there is no Markush group in Claim 48.

For the foregoing reasons, the Examiner is asked to withdraw this rejection.

D. Section 103 Rejection

Claims 48-53, 56-58, 60-61, 63-64 and 66-68 have been rejected as being unpatentable over U.S. Patent No. 5,227,307 (Bar-Or et al.) in view of U.S. Patent No. 5,994,339 (Crapo et al.) and U.S. Patent No. 6,375,930 (Young et al.). Applicants respectfully traverse this rejection.

The claims of the present application are directed to a method of monitoring or assessing treatment of a disease or condition with a drug that produces or reduces free radicals. This is done by quantitating albumin which is modified at its N-terminus in a manner that results in a reduction in the ability of the modified albumin to bind metal ions at its N-terminus.

Bar-Or et al. describe a method of detecting ischemia by contacting a patient sample with a metal ion that is capable of binding to proteins in the sample which contain thiol groups (see, *e.g.*, column 1, lines 9-11, and column 4, lines 49-54). Unbound metal ions are measured, and an increased amount of unbound metal ions is diagnostic of an ischemic event. Bar-Or et al. hypothesize that the number of thiol groups on the proteins in the sample is reduced by free radicals produced as a result of an ischemic event (see, *e.g.*, column 2, line 57, through column 3, line 11, of Bar-Or et al.). Bar-Or et al. further hypothesize that the reduction in the number of thiol groups results in a reduction in the amount of metal ions bound by the proteins in a given sample, explaining why an increased amount of unbound metal ions provides a means of detecting an ischemic event.

Bar-Or et al. do not teach or suggest monitoring or assessing the effectiveness of treatment of patients with drugs that produce or reduce free radicals. Bar-Or is directed to the diagnosis of one specific condition - ischemia (see, *e.g.*, column 1, lines 7-11, column 2, lines 33-45, of Bar-Or et al.). The fact that oxidative damage might be the cause of the reduced metal binding that is diagnostic of ischemia is only a hypothesis (see column 3, lines 6-11, of Bar-Or et al.). Accordingly, those skilled in the art would not have been motivated to use the method of Bar-Or et al. to do anything other than diagnose ischemia.

While Bar-Or et al. mention other possible binding sites for metal ions on proteins besides the thiol groups (see column 3, lines 14-26, of Bar-Or et al.), only the thiol groups are believed to be altered as a result of the production of free radicals during ischemic events (see column 2, line 57, through column 3, line 11, of Bar-Or et al.). In particular, Bar-Or et al. do not teach or suggest that the N-terminus of albumin binds metal ions, that the metal-binding capacity of the N-terminus of

albumin would be altered by free radicals, or that the N-terminus of albumin would be a relevant site for assessing free radical damage.

As noted above, Bar-Or et al. teach the measurement of unbound metal ions to detect the occurrence or nonoccurrence of an ischemic event. Claims 48-59 of the present application are directed to measuring bound metal ions. Nothing in Bar-Or et al. teaches or suggests measuring bound metal ions, since a specific metal-binding site was not contemplated in contrast to the present invention.

Crapo et al. and Young et al. do teach the treatment of diseases with, respectively, antioxidants (*e.g.*, oxidant scavengers) or vesicles comprising a photosensitive agent which provides for lysis of the vesicles when irradiated. However, neither reference teaches or suggests monitoring or assessing the effectiveness of treatment with these materials using a test like that described in Bar-Or et al. As noted above, there is no teaching or suggestion in Bar-Or et al. to use the method described in Bar-Or et al. to do anything other than diagnose ischemia. In particular, there is no teaching or suggestion in Bar-Or et al. to use the method of Bar-Or et al. to monitor or assess the effectiveness of drugs that produce or reduce free radicals. Thus, there is no basis for combining the teachings of the cited references, and it is submitted that the Examiner has improperly reconstructed the invention through hindsight, which the Examiner must not do.

For all of the foregoing reasons, the cited references would not have made the present invention obvious. Consequently, it is respectfully requested that the Examiner withdraw this rejection.

E. Information Disclosure Statements

Enclosed are duplicate copies of the PTO 1449 forms for the Information Disclosure Statements received July 27, 2001 and November 14, 2001 by the Examiner. In view of the significant expense associated with providing duplicate copies of the references, Applicants hereby request that the Examiner attempt again to access parent application No. 90165,961 to review the references listed on these PTO 1449 forms. Applicants make note of 37 CFR §1.98(d), which specifically allows an Applicant to make reference to a related application rather than supplying duplicate copies of cited references.

CONCLUSIONS

It is submitted that the pending claims are in condition for allowance, and a speedy allowance of them is requested.

Respectfully submitted,

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VERSION OF AMENDMENTS WITH MARKINGS TO SHOW CHANGES MADE

In the Specification:

On page 1, the section entitled "Cross Reference to Related Application" has been replaced as follows:

CROSS REFERENCE TO RELATED APPLICATION

The present application is a continuation of pending PCT application PCT/US99/22746, filed October 1, 1999, which is a continuation-in-part of pending U.S. application Serial No. 09/165,961, filed October 2, 1998, the entire contents of both of which are incorporated herein by this reference. PCT application PCT/8S99/22746 claims priority from U.S. application Serial No. 09/165,961 and from U.S. provisional application Serial No. 60/102,962, also filed on October 2, 1998.

In the Claims:

48. (Amended Once) A method of monitoring or assessing treatment of a disease or condition with a compound that produces or reduces free radicals comprising:

obtaining a first biological sample [containing albumin] from a patient suffering from the disease or condition, the biological sample containing albumin and possibly containing a modified albumin having a reduced ability to bind metal ions at its N-terminus;

treating the patient with the compound;

obtaining one or more additional biological samples of the same type from the same patient at one or more times after the treatment; and

determining if there is a change in the quantity of the [a] modified albumin present in the first sample as compared to the subsequent sample(s), [the modified albumin having a reduced ability to bind metal ions at its N-terminus,] the quantity of the modified albumin in each sample being indicative of the amount of free radical damage in that sample, and a change in the quantity of the modified albumin in the first sample as compared to the subsequent sample(s) being indicative of a change in the amount of free radical damage and, therefore, of the effectiveness or ineffectiveness of the treatment, the determination being made by:

(a) contacting each of the biological samples with an excess quantity of a metal ion salt, the metal ion being capable of binding to the N-terminus of unmodified human albumin, to form a mixture of bound metal ions and unbound metal ions;

(b) determining the amount of bound metal ions for each biological sample, the amount of bound metal ions providing a measure of the quantity of the modified albumin in the sample; and

(c) determining if there is a change in the amount of bound metal ions between the first and subsequent sample(s), the change in the amount of bound metal ions providing a measure of the change in the quantity of the modified albumin between the first and subsequent sample(s).